UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KEIICHI KAWAI, NORITO TAKAMURA and RYUICHI NISHII

Appeal No. 2005-2383
Application No. 10/018,745

HEARD: October 6, 2005

Before ELLIS, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of regulating the bioavailability of a drug by administering it in combination with a second drug. The examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

"Generally, drugs administered for the purpose of medical treatment or diagnosis once go through the systemic blood circulation, and then take the process of absorption, distribution, metabolism, excretion and the like. . . . When movement of the drug reaches a steady state, then the free drug concentration in each space become[s]

uniform, thus the whole pattern of the concentration of the drug is determined by the binding level with proteins." Specification, pages 1-2.

The specification discloses a method of regulating the amount of free drug in a patient – i.e., drug unbound to plasma proteins – by administering the drug in combination with a second drug that binds to the same plasma protein as the first drug.

> For example, [a drug known as ^{99m}Tc-MAG$_3$] is widely used in renal scintigraphy. . . . It is known that about 90% of ^{99m}Tc-MAG$_3$ binds to plasma protein in an ordinary clinical dose. . . . If the binding of ^{99m}Tc-MAG$_3$ with plasma protein is inhibited by drugs having high binding affinity to the same binding site on protein with ^{99m}Tc-MAG$_3$, then more clear renal imaging can be obtained.

Page 2.

More generally, "[w]hen the second drug having high binding affinity for the same plasma protein, for which the first drug has binding affinity, is administered simultaneously with the first drug, or before or after the administration of the first drug, then competitive displacement will take place at the binding site, thus it can be thought that the first drug may be released in a higher concentration (displacement effect). Therefore, it can be expected that the higher pharmacological activity of the first drug can be obtained as compared with the case that the first drug is administered singly." Page 7.

"Generally, as the plasma proteins bound to drug, human serum albumin (HSA), α_1-acidic glycoprotein (AGP), γ-globulin, lipoprotein and the like are exemplified, and many drugs may bind to HSA or AGP. . . . When the first drug has the property of binding to AGP, it may be preferably selected from a basic drug having the binding

affinity for AGP." Page 10. Drugs with binding affinity for AGP include disopyramide, verapamil, and propranolol. Page 12.

Discussion

1. Claim construction

Claims 14-19 and 21-27 are pending and on appeal. Claims 14 and 21 are the only independent claims and read as follows:

14. Method of in-vivo administration of drugs with binding affinity for plasma protein, which is characterized in that, in the administration of a first drug with binding affinity for plasma protein, verapamil as a second drug with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein.

21. A pharmaceutical preparation for regulating binding affinity of a first drug for plasma protein, which comprises a first drug with binding affinity for plasma protein and verapamil as a second drug with binding affinity for the same plasma protein, for which the first drug has binding affinity.

Thus, claim 14 is directed to a method comprising administering verapamil and a "first drug" with binding affinity for the same plasma protein, either simultaneously or sequentially, "to thereby regulate the binding of the first drug to the plasma protein." Claim 21 is directed to a "pharmaceutical preparation" comprising a combination of verapamil and a "first drug" with binding affinity for the same plasma protein.

2. Anticipation

The examiner rejected claims 14-17, 21, 23, and 25 as anticipated by Somogyi.[1] The examiner pointed to Somogyi's experiment in which "[a]n intravenous (unlabeled) dose of verapamil in HCl and saline was administered in combination with an oral dose

[1] Somogyi et al., "Pharmacokinetics, Bioavailability and ECG Response of Verapamil in Patients With Liver Cirrhosis," Br. J. Clin. Pharmacol., Vol. 12, pp. 51-60 (1981).

of d_3-verapamil (trideuterated verapamil at the methoxy group of the benzene ring para to the quaternary carbon atom)." Examiner's Answer, page 4. The examiner noted that "Appellant's [sic] independent claims do not specify that the various derivatives of a drug may not be administered as the first and second drugs." Id., page 5.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "'Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.'" In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) (quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)) (emphasis and bracketed material in original).

Somogyi discloses a study aimed at "investigat[ing] the influence of liver cirrhosis on the pharmacokinetics and bioavailability of verapamil using a stable labelled oral solution and simultaneous administration of an unlabelled intravenous dose of the drug, thus minimizing patient inconvenience." Page 51, right-hand column. That is, Somogyi performed two experiments simultaneously in the same patients: measuring the pharmacokinetics of orally administered verapamil using d_3-labelled verapamil, and measuring the pharmacokinetics of intravenously administered verapamil using unlabelled verapamil.

Somogyi administered 10 mg of unlabelled verapamil to patients intravenously, then orally administered either 40 mg or 80 mg of d_3-verapamil. Page 52, left-hand column. The results for the intravenously administered, unlabelled verapamil are shown in Figure 1(a) and Table 2; the results for the d_3-verapamil are shown in Figure 1(b) and Table 3.

In a separate experiment, the protein binding of verapamil was determined. This experiment was carried out in vitro using "a blood sample taken prior to verapamil administration. The binding was determined at four different concentrations, 10, 25, 50 and 100 ng/ml of plasma, by equilibrium dialysis using [^{14}C]-verapamil." Page 52, right-hand column. Somogyi found that

> [i]n the liver cirrhotic patients, the free fraction of verapamil in plasma was on average 8.0 . . . % and was independent of the total verapamil concentration. . . . This free fraction was not different to those reported by us (range 7.8 to 11.3%) previously.

Paragraph bridging pages 54 and 55. Thus, Somogyi found that an average of 92% of the verapamil in plasma was bound to plasma proteins (8% free = 92% bound), and this percentage was the same whether the verapamil was present in the plasma at 10 ng/ml or 100 ng/ml.

We agree with the examiner that different forms of the same drug are within the scope of the "first drug" and "second drug" recited in the instant claims. The specification does not define any particular attributes that distinguish the claims' "first drug" and "second drug." Claims are given their broadest reasonable interpretation, consistent with the specification, during examination. See In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Therefore, it is reasonable to interpret

the claims as encompassing different forms of the same drug – e.g., unlabelled verapamil and labelled verapamil – as the recited "first drug" and "second drug."

We also agree with the examiner that two forms of the same drug can compete for binding to the same sites, even though they bind with the same affinity, and that such competition would meet the claim limitation requiring "regulat[ing] the binding of the first drug." See the Examiner's Answer, page 7.

However, we do not agree that such competition is actually shown by Somogyi. Competition for binding sites will only take place when the number of sites is limited compared to the number of molecules available to bind them. That is, when the number of drug molecules is small relative to the number of available binding sites, there will not be competition for binding sites because most of the binding sites will be empty at any given time.

That is the situation described by Somogyi. Somogyi discloses that 92% of the verapamil in plasma was protein-bound regardless of whether the concentration of verapamil was 10 ng/ml or 100 ng/ml. This result indicates that, at least up to plasma concentrations of 100 ng/ml, verapamil molecules were not competing for plasma protein binding sites: if such competition had taken place, the percentage of protein-bound verapamil would have decreased at higher concentrations.

That is, if competition is taking place (e.g., between labelled and unlabelled verapamil), some molecules will be excluded from binding sites because those sites are already occupied by other molecules; the out-competed drug molecules remain free even though they would have become protein-bound if the binding site had been open. Therefore, the percentage of free molecules is increased under conditions where there

is competition for binding sites. Somogyi's results, that the percentage of protein-bound verapamil was the same at all tested concentrations, indicate that no competition for binding sites takes place at those concentrations.

The concentrations used to assess verapamil's protein-binding (up to 100 ng/ml) appear to be reasonably reflective of in vivo concentrations of verapamil. See Figures 1(a) and 1(b). In healthy patients, measured plasma verapamil levels did not exceed 50 ng/ml, although in liver cirrhotic patients plasma verapamil levels did transiently exceed 100 ng/ml, and reached as high as 400 ng/ml with orally administered verapamil. Even this level, however, is only four times higher than the concentrations used in the in vitro protein-binding experiment. The examiner has not provided any basis on which to conclude that labelled verapamil will affect plasma protein binding of unlabelled verapamil at a concentration of 400 ng/ml, even though no effect is seen at 100 ng/ml.

Thus, while we agree with the examiner that the experiment taught by Somogyi could potentially meet the limitations of claim 14, we do not agree that it in fact does meet those limitations. We also do not agree with the examiner's assertion that the claim is anticipated because Somogyi teaches that patients were administered cimetidine, indocyanine green; or spironolactone (see the Examiner's Answer, pages 4-5): the examiner has cited no evidence to show that any of these drugs bind to the same plasma protein(s) as verapamil. Nor has the examiner pointed to any "pharmaceutical preparation" disclosed by Somogyi that comprises verapamil in combination with another drug that binds the same plasma protein. The rejection under § 102 is reversed.

3. Obviousness

The examiner rejected claims 14, 16-19, and 21-27 under 35 U.S.C. § 103 as obvious in view of Somogyi and Li.[2] The examiner, however, relied on Li only to meet the limitations of certain dependent claims. See the Examiner's Answer, pages 5-6. The examiner has not explained how Li would have suggested the limitations of claim 14 or claim 21 that are missing from Somogyi. The rejection under 35 U.S.C. § 103 is reversed for the reasons discussed above.

Summary

Somogyi does not disclose a method in which verapamil "regulate[s] the binding" of another drug to plasma proteins, or a pharmaceutical preparation comprising verapamil and another drug that binds the same protein(s). Li does not make up for the deficiencies of Somogyi. The rejections under 35 U.S.C. §§ 102 and 103 are therefore reversed.

REVERSED

JOAN ELLIS
Administrative Patent Judge)
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DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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ERIC GRIMES) INTERFERENCES
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[2] Li et al., U.S. Patent 5,977,163, issued Nov. 2, 1999.

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